(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 388 691 A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 90104125.1

(22) Date of filing: 02.03.90

(51) Int. Cl.[5]: C07D 401/04, A61K 31/415, A61K 31/44

(30) Priority: 22.03.89 US 327219

(43) Date of publication of application: 26.09.90 Bulletin 90/39

(84) Designated Contracting States: AT BE CH DE DK ES FR GB GR IT LI NL SE

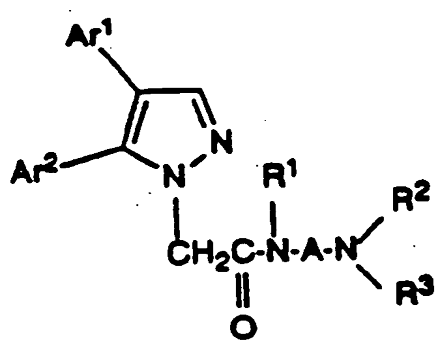
(71) Applicant: STERLING DRUG INC.
90 Park Avenue
New York New York(US)

(72) Inventor: Bailey, Denis Mahlon
233 Lindenwood Drive
Exton, Pennsylvania 19341(US)
Inventor: D'Ambra, Thomas Edward
14 Woodside Court
Wynantskill, New York 12198(US)
Inventor: Ezrin, Alan Mark
17 Alpine Drive
Latham, New York 12110(US)

(74) Representative: Baillie, Iain Cameron et al
c/o Ladas & Parry Isartorplatz 5
D-8000 München 2(DE)

(54) Azole-1-alkanamides as antiarrhytmic agents and preparation thereof.

(57) N-[(alkylkamino)alkyl]-4,5-diaryl-1H-pyrazole-1-acetamides of formula



or acid-addition salt thereof wherein R^1 is hydrogen or lower-alkyl; R^2 and R^3 are independently hydrogen, lower-alkyl, or hydroxy lower-alkyl, or R^2 and R^3 together form a straight or branched alkylene chain of four to six carbons; A is $CH_2CH(OH)CH_2$ or $(CH_2)_n$ wherein n is an integer from two to eight; Ar^1 and Ar^2 are independently pyridinyl, phenyl, or phenyl substituted with methoxy, hydroxy or halogen; and at least one of Ar^1 and Ar^2 is pyridinyl, useful for treating cardiac arrhythmias in mammals, are prepared by reacting a

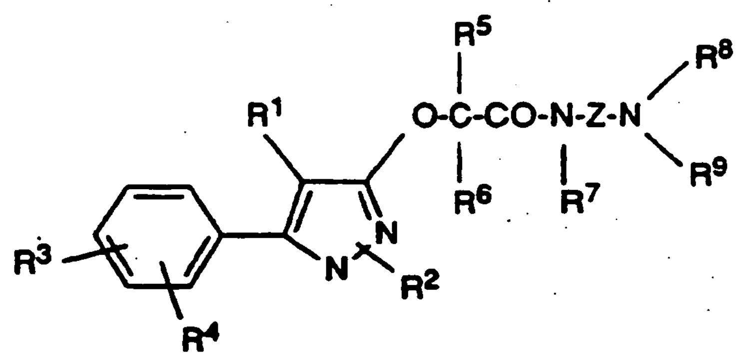
EP 0 388 691 A1

lower-alkyl ester of pyrazole-1-acetic acid with an appropriate diamine.

The present invention relates to novel N-[(alkylamino)-alkyl]-4,5-diaryl-1H-pyrazole-1-acetamides, and the preparation thereof for treating cardiac arrhythmia in mammals utilizing said pyrazole-1-acetamides.

Information Disclosure Statement

U.S.Patent 4,695,566 to Heinemann et al. discloses as antiarrythmic agents 1H-pyrazol-3-yl(and 1H-pyrazol-5-yl) oxyacetamides of general formula



Specifically disclosed are (1) N- [2-(diethylamino)ethyl]-2-[(5-phenyl-1H-pyrazol-3-yl)oxy]acetamide, example 5, and (2) N-[3-(diethylamino)propyl]-2- [(5-phenyl-1H-pyrazol-3-yl)oxy]acetamide, example 24.

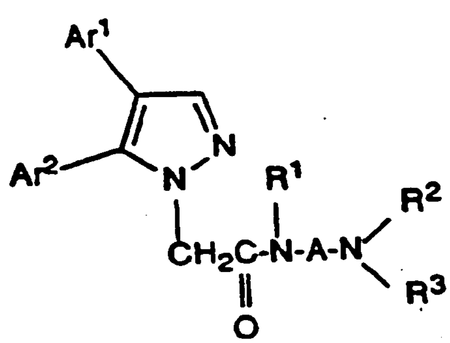
U.S. Patent 4,182,895 to Bailey discloses as an intermediate in the synthesis of 1-amino-lower-alkyl-3,4-diphenyl-1H-pyrazoles "β-[1-(3,4-diphenyl-1H-pyrazolyl)]-N,N-dimethylpropionamide" at column 8, line 63 to 64.

U.S. Patent 4,072,498 to Moon and Kornis discloses N,N,α,α,-tetramethyl-3,4-diphenylpyrazole-1-acetamide (example 160) and N,N,α-trimethyl-5-(2-thienyl)pyrazole-1-acetamide (example 29)as herbicides.

Ezrin et al. [FASEB Journal 2,- A1557(1988)]describes the antiarrhythmic activity of N-[3-(diethylamino)propyl]-4,5-diphenyl1H-pyrazole-1-acetamide fumarate.

European patent application 299,407, published January 18,1989 discloses a series of 4,5-diaryl-1H-pyrazole-1-alkanamides as antiarrhythmic agents.

The present invention relates to compounds of the formula I



I

or acid-addition salt thereof wherein R[1] is hydrogen or lower-alkyl; R[2] and R[3] are independently hydrogen, lower-alkyl, or hydroxy lower-alkyl, or R[2] and R[3] together form a straight or branched alkylene chain of four to six carbons; A is $CH_2CH(OH)CH_2$ or $(CH_2)_n$ wherein n is an integer from two to eight; Ar[1] and Ar[2] are independently pyridinyl, phenyl, or phenyl substituted with methoxy, hydroxy or halogen; and at least one of

Ar^1 and Ar^2 is pyridinyl.

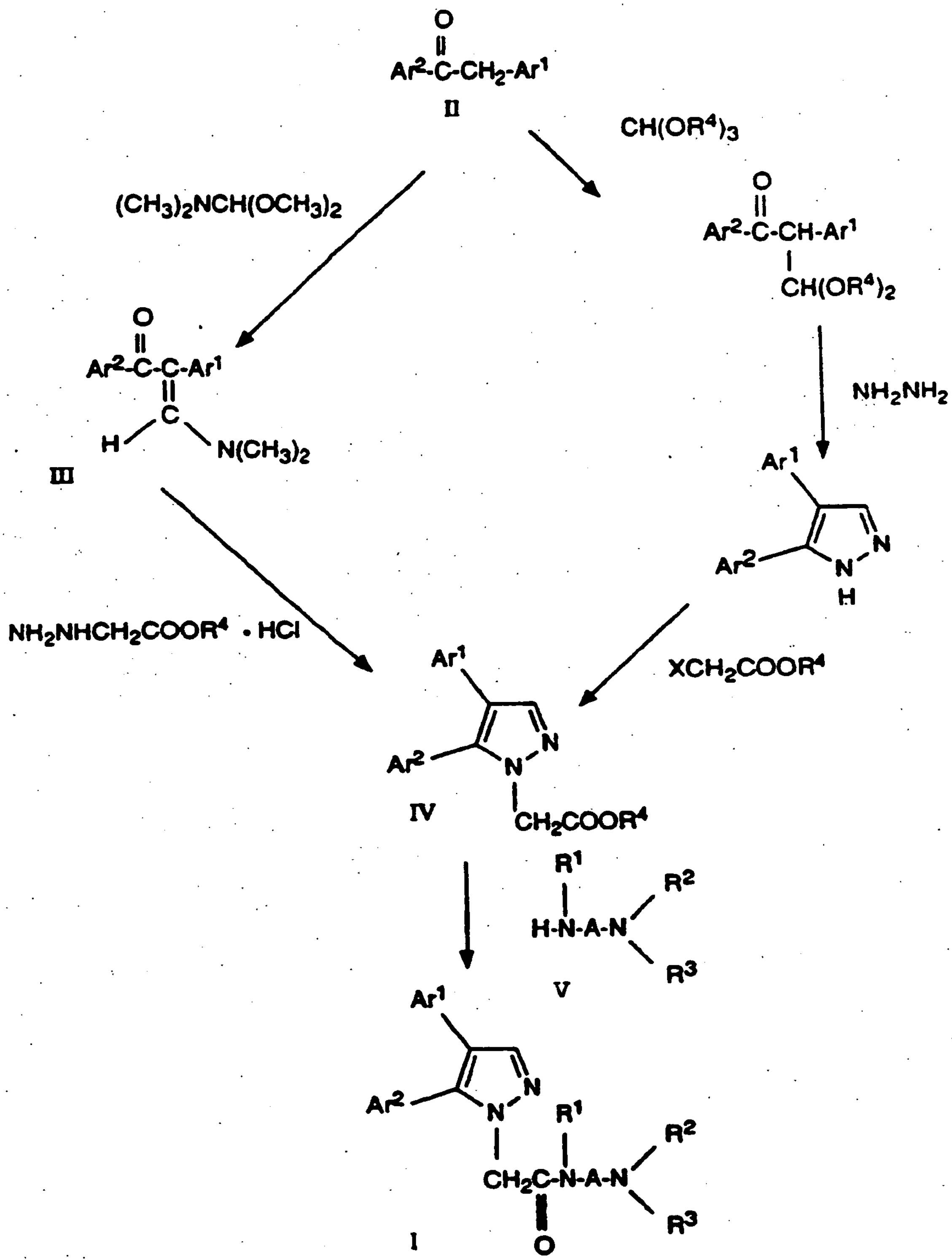
Lower-all as used herein describes linear or branched hydrocarbon chains of four or fewer carbon atoms; lower-alkoxy as used herein describes linear or branched alkyloxy substituents containing four or fewer carbon atoms; halogen describes bromine, chlorine or fluorine.

Compositions for treatihg cardiac arrhythmia comprise compounds of the formula I together with pharmaceutically acceptable excipients or diluents as required. One can treat cardiac arrhythmia in a mammal by administering to said mammal an antiarrhymically effective amount of a compound of formula I.

Processes for preparing a compound of formula I comprise reacting a pyrazole-1-acetate or a pyrazole-1-acetic acid with an amine.

The synthesis of compounds of the invention may be outlined as shown in scheme A within R^4 is lower-alkyl or hydrogen

SCHEME A


O
Ar2-C-CH2-Ar1
II
CH(OR4)3
O
Ar2-C-CH-Ar1
CH(OR4)2
(CH3)2NCH(OCH3)2
O
Ar2-C-C-Ar1
C
H
N(CH3)2
III
NH2NH2
Ar1
Ar2
N
N
H
NH2NHCH2COOR4 · HCl
XCH2COOR4
Ar1
Ar2
N
N
IV
CH2COOR4
R1
R2
H-N-A-N
R3
V
Ar1
Ar2
N
N
R1
R2
CH2C-N-A-N
R3
I
O

An appropriately substituted diarylethanone (II) is reacted with an excess, preferably about 10% excess, of dimethylformamide dimethylacetal in an inert solvent, preferably methyl t-butyl ether, at 20° to 100° C, preferably 53-56° C. The diaryl ethanone may be synthesized by the procedure of Nahm and Weinreb (Tet. Lett. 1981,3815-3818) from the appropriate acid and the appropriate hetaryllithium or hetarylmethyl lithium species via the N-methoxy-N-methyl amide of said acid.

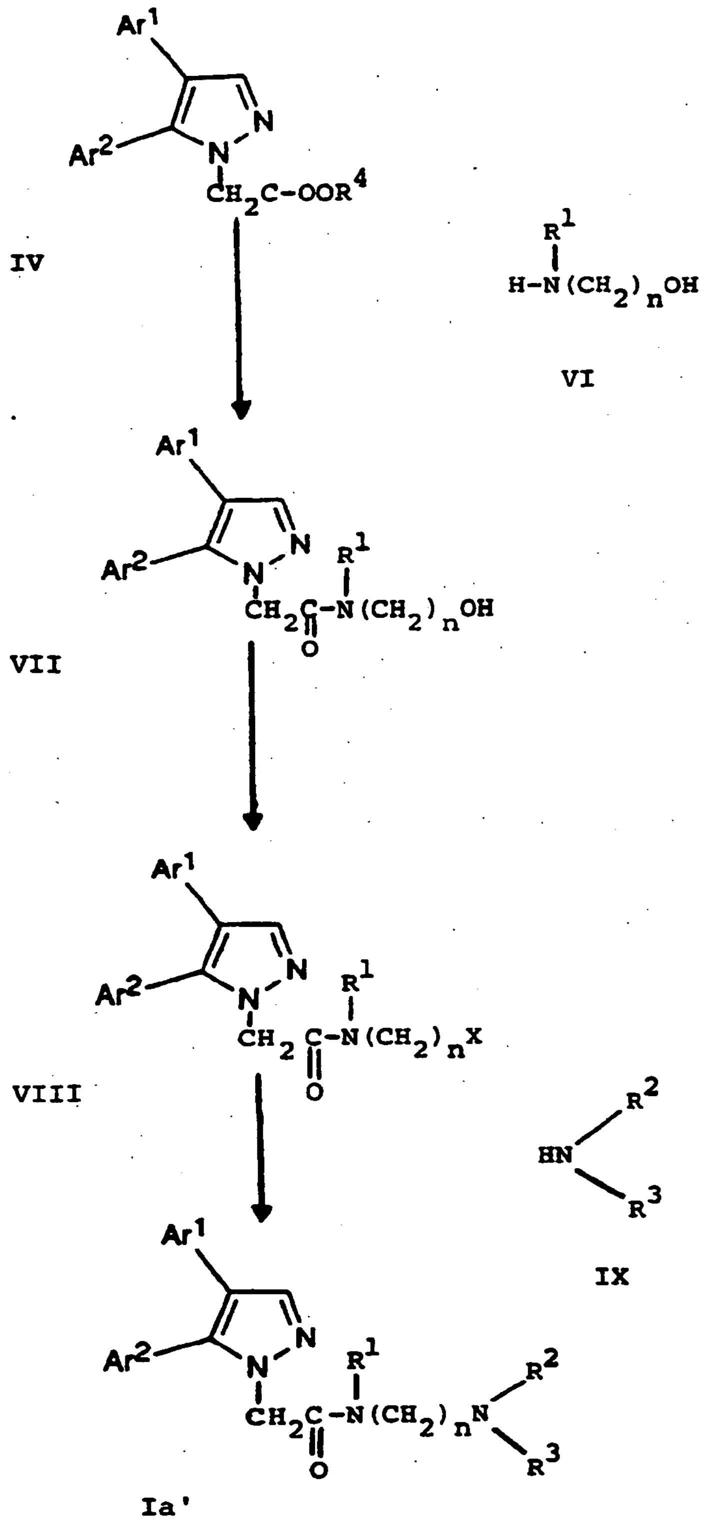
The β-ketoenamine (III) resulting from the reaction of diarylethanone and DMF acetal is reacted with the salt of a lower-alkyl hydrazinoacetate, preferably ethyl hydrazinoacetate hydrochloride in a suitable solvent, preferably ethanol, at 20-100° C, preferably 40-50° C, to yield substantially pure 4,5-diaryl-1H-pyrazole-1-acetate of formula IV.

Alternatively, in those cases where the diarylethanone appears to exist primarily as its enol tautomer, the diarylethanone is reacted with an orthoformate ester and a Lewis acid, preferably ethyl orthoformate and boron trifluoride etherate, in an inert solvent, preferably methylene chloride, at -78° to 0° C to form a 3,3-dialkoxy-1-propanone. The propanone is reacted with hydrazine at 0° to 100° C, preferably at about 78° C in a suitable solvent, preferably ethanol, to provide a 3,4-(4,5-)diaryl-1H-pyrazole. The pyrazole is converted to the pyrazole1-acetate by alkylation with an α-haloacetate ester (X is Cl or Br), preferably ethyl chloroacetate, using a base, preferably sodium hydride, in an inert solvent, preferably DMF, at 0° to 100° C, preferably at room temperature.

The lower-alkyl ester, preferably a methyl or ethyl ester, of the suitably substituted 4,5-diarylpyrazole-1-alkanoic acid (V) is reacted with an excess of a primary or secondary amine of formula V at 20° to 150° C, preferably at 90 to 100° C. When the amine is valuable, the ester IV is preferably reacted with about one equivalent of the amine v in the presence of a tertiary amine, preferably diisopropylethylamine, optionally in an inert solvent.

Alternatively, the compounds of the invention wherein A is $(CH_2)_n$ may be synthesized as outlined in Scheme B:

Scheme B


Ar1
Ar2
N
N
CH2C-OOR4
IV
R1
H-N(CH2)nOH
VI
CH2C-N(CH2)nOH
O
VII
CH2C-N(CH2)nX
VIII
HN
R2
R3
IX
CH2C-N(CH2)nN
Ia'

A lower-alkyl ester, preferably a methyl or ethyl ester, of a suitably substituted 4, 5-diaryl-1H-pyrazole-1-alkanoic acid (IV) is reacted with an excess of a primary or secondary ω-aminoalkanol (VI) optionally in the presence of an external base at 20-150° C., preferably at 90-100° C., to produce an N-[ω-hydroxyalkyl]-pyrazole-1-alkanamide of formula VII. The hydroxyalkylalkanamide (VII) is activated preferably by sulfonylation, preferably with methanesulfonyl chloride, in the presence of a base/solvent such as pyridine at -20° to 20° C., preferably at 0° C., to produce an alkylalkanamide of formula VIII wherein X is a group which is subject to nucleophilic displacement such as toluenesulfonate or methanesulfonate, that is, OSO_2R_8 where R_8 is alkyl or aryl, e.g., toluyl or methyl. Alternatively, the hydroxyalkyl-alkanamide (VII) is converted to the corresponding halide (VIII, X = Cl, Br or I) by phosphorus trihalide, phosphorus pentahalide, thionyl halide or tetrahalomethane with trialkylphosphine. The group X is then displaced by reaction in the presence or absence of solvent with an appropriate primary or secondary amine (IX) at 20° to 100° C.

Alternatively, the compounds of the invention be synthesized from the free acids, which can be obtained by hydrolysis of the corresponding esters. Thus a suitably substituted 4,5-diaryl-1H-pyrazole-1-acetic acid (IV wherein R^4 is hydrogen) is activated by procedures well-known in the art, such as reaction with an acid chloride to form a mixed anhydride, reaction with a carbodiimide to form an O-acylisourea, or reaction with carbonyl diidazole to form an imidazolide. The activated acid in an inert solvent is then combined at -20° to 75° C. with a stoichiometric amount or a slight excess of a primary or secondary amine of formula V or ω-aminoalkanol of formula VI.

The compounds of formula I are useful both in the free base form and the form of acid-addition salts, and both forms are within the purview of the invention. The acid-addition salts are in some cases a more convenient form for use, and in practice the use of the salt form inherently amounts to the use of the base form. The acids which can be used to prepare the acid-addition salts include preferably those which produce, when combined with the free base, medicinally acceptable salts that is, salts whose anions are relatively innocuous to the animal organism in medicinal doses of the salts so that the benefical properties inherent in the free base are not vitiated by side effects ascribable to the anions. In practicing the present invention it is convenient to form the hydrochloride, fumarate, toluenesulfonate, methanesulfonate, or maleate salts. However, other appropriate medicinally acceptable salts within the scope of the invention are those derived from other mineral acids and organic acids. The acid-addition salts of the basic compounds are prepared either by dissolving the free base in aqueous alcohol solution containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and an acid in an organic solvent, in which case the salt separates directly, is precipitated with a second organic solvent, or can be obtained by concentration of the solution. Although medicinally acceptable salts of the basic compounds are preferred, all acid-addition salts are within the scope of the present invention as well as solvates, e.g., hydrates, of the compounds formed. All acid-addition salts are useful as sources of the free base form even if the particular salt per se is desired only as an intermediate product, as, for example, when the salt is formed only for purposes of purification or identification, or when it is used as an intermediate in preparing a medicinally acceptable salt by ion exchange procedures.

The structures of the compounds of the invention were established by the mode of synthesis, by elemental analysis, and by infrared, ultraviolet, and nuclear magnetic resonance, spectroscopy. The course of the reactions and the identity and homogeneity of the products were assessed by thin layer chromatography (TLC) or gas-liquid chromatography (GLC). The starting materials are either commercially available or may be prepared by procedures well known in the art.

In the following procedures melting points are given in degrees C and are uncorrected. The abbreviation THF stands for tetrahydrofuran, DMF stands for N,N-dimethylformamide and Ac stands for the acetyl residue, CH_3CO.

General Procedure 1

N-methoxy-N-methylamides

To solution of 1 equivalent of the appropriate acid chloride in methylene chloride was added 1.2 equivalents of solid methoxymethylamine hydrochloride. 2.5 equivalents of triethylamine was added at about 0° C and the reaction was stirred at room temperature for 48 hours. The triethylamine hydrochloride was filtered off, the methylene chloride solution was washed with water, dried and stripped to yield the

amide as an oil.

By this procedure were made (1) N-methoxy-N-methyl-3-pyridinecarboxamide, (2) N-methoxy-N-methylbenzenacetamide, (3) N-methoxy-N-methylbenzamide and (4) N-methoxy-N-methyl-2-pyridinecarboxamide.

General Procedure 2

Desoxybenzoin Analogs

A solution of 1.2 equivalents of the appropriate picoline or bromopyridine in ether at -78°C under nitrogen was treated with 1 equivalent of N-butyllithium in hexane and then stirred one hour without cooling to generate the anion. The reaction was again cooled to -78°C and an ether solution containing 1 equivalent of the appropriate N-methoxy-N-methylamide from procedure 1 was added dropwise. After the addition was complete the reaction was allowed to come to room temperature and stirred for 3 hr. Any excess butyllithium was quenched with isopropyl alcohol at -78°C, water was added at room temperature, and the ether was stripped off. The product was treated with excess 0.25M NaOH, extracted into methylene chloride, and stripped.

By this procedure were obtained (1) 1,2-bis(2-pyridinyl)ethanone, (2) 1-(3-pyridinyl)-2-(2-pyridinyl) ethanone, (3) 2-phenyl-1-(3-pyridinyl)ethanone, (4)1-phenyl-2-(2-pyridinyl)ethanone.

Example 1

Ethyl-5-phenyl-4-(2-pyridinyl)-1H-pyrazole-1-acetate

A solution of 26g (0.132 mol) of 1-phenyl-2-(2-pyridinyl)ethanone and 19.3 mL (0.145 mol) of dimethylformamide dimethylacetal in 100 mL of methyl t-butyl ether was refluxed 4 hr. Because TLC on silica gel with 10% isopropylamine in ethyl acetate showed little reaction, another 20 mL of DMF dimethylacetal was added and the solution refluxed a further 6 hr. The solvent was stripped and the resulting crude, oily β-ketoenamine was dissolved in 400 mL of ethanol. The ethanol solution was heated to 40° with 22g (0.143 mol) of ethyl hydrazinoacetate hydrochloride for about 1.5 hr. The solvent was stripped, and the resulting impure product was dissolved in a small amount of methylene dichloride and applied to a column of 850g of silica gel. The column was eluted with 2:1 hexane-ethyl acetate to yield 25g of yellow solid product, mp 98-100°C after evaporation of the solvent.

Example 2

Ethyl 4-phenyl-5-(3-pyridinyl)-1H-pyrazole-1-acetate

By a process substantially similar to that of example 1, 23g of ethyl 4-phenyl-5-(3-pyridinyl)-1H-pyrazole-1-acetate, mp 90-91°C from cyclohexane, was obtained from 29g (0.147 mol) of 2-phenyl-1-(3-pyridinyl)ethanone, 21.5 mL (0.162 mol) of DMF dimethylacetal and 20.6g (0.133 mol) of ethyl hydrazinoacetate hydrochloride.

Example 3

Ethyl 4-(2-pyridinyl)-5-(3-pyridinyl)-1H-pyrazole-1-acetate

By a process substantially similar to that of example 1, 9g of ethyl 4-(2-pyridinyl)-5-(3-pyridinyl)-1H-pyrazole-1-acetate, mp 43-46° C, was obtained from 11.0g (0.055 mol) of 1-(3-pyridinyl)- 2-(2-pyridinyl)-ethanone, 8.1 mL (0.061 mol) of DMF dimethylacetal and 9.8g (0.064 mol) of ethyl hydrazinoacetate hydrochloride. The chromatographic purification utilized 3:1 hexane-acetone in place of the 2:1 hexane-ethyl acetate of example 1.

Example 4

Ethyl 4,5-bis(2-pyridinyl)-1H-pyrazole-1-acetate

A solution of 15 mL (0.089 mol) of triethyl orthoformate in 100 mL of methylene chloride was stirred under nitrogen at -78° C and 13.2 mL (0.108 mol) of boron trifluoride etherate was added. The solution was allowed to warm to 0° C, recooled to -78° C, and a solution of 8.0g (0.04 mol) of 1,2-bis(2-pyridinyl)-ethanone in 75 mL of methylene chloride was added, followed after 30 min by 22 mL (0.132 mol) of diisopropylethylamine in 30 mL of methylene chloride. The reaction was stirred 45 min at -78° C, poured into 400 mL of water containing 10 g of $NaHCO_3$ and stirred 20 min. The phases were separated, the methylene chloride layer was dried over $MgSO_4$ and stripped to yield about 17g of crude 3,3-diethoxy-1,2-bis(2-pyridinyl)-1-propanone.

The propanone was dissolved in 1L of ethanol, 5.8mL (0.12 mol) of hydrazine hydrate was added, and the mixture was heated to reflux for 1 hr. The ethanol was stripped off in vacuo, and the residue was put through a 600g silica gel column eluting with 1:1 hexane-acetone to yield about 4g of 4,5-bis(2-pyridinyl)-1H-pyrazole as a light tan solid after removal of solvent.

The 4g of pyrazole was added to a suspension of 0.52g (21.6 mmol) of sodium hydride (0.86g of a 60% dispersion in oil) in 50mL of DMF. The mixture was stirred 15 minutes and 2.3mL (21.6 mmol) of ethyl chloroacetate was added. After 30 minutes water was added cautiously to destroy any excess sodium hydride. The solvent was removed in vacuo, the residue was partitioned between ethyl acetate and water, and the organic layer was dried and stripped to a yellow oil. The oil was dissolved in 1:1 acetone-hexane and filtered through silica gel to yield 4g of ethyl 4,5-bis(2-pyridinyl)-1H-pyrazole-1-acetate as an oil containing about 5% of an impurity.

Example 5

N-[3-(Diethylamino)propyl]-5-phenyl-4-(2-pyridinyl)-1H-pyrazole-1-acetamide

A solution of 10g (0.032 mol) of ethyl 5-phenyl-4-(2-pyridinyl)pyrazole-1-acetate of example 1 in 15 mL (0.095 mol) of 3-(diethylamino) propanamine was heated at 100° for 3 hr. The excess amine was stripped in vacuo and the residue distributed between water and ether. The ether solution was dried over Mg SO_4, stripped and applied to 350g of silica gel in a small amount of methylene chloride. The column was eluted with 20:1 acetone-triethylamine and a light yellow oil was obtained that crystallized upon triturating with cyclohexane to yield 5.4g of product, mp 82-83° C.

Example 6

N-[3-(Diethylamino)propyl]-4-phenyl-5-(3-pyridinyl-1H-pyrazole-1-acetamide hemihydrate

By procedure substantially similar to that of example 5, 6.7g of N-[3-(diethylamino)propyl]-4-phenyl-5-(3-pyridinyl)-1H-pyrazole-1-acetamide hemihydrate, mp 61-62° C was obtained from 10g (0.032 mol) of ethyl 4-phenyl-5-(3-pyridinyl)-1H-pyrazole-1-acetate of example 2 and 15 mL(0.096 mol) of 3-(diethylamino)-propanamine.

Example 7

N-[3-(Diethylamino)propyl]4-(2-pyridinyl)-5-(3-pyridinyl)-1H-pyrazole-1-acetamide dihydrochloride

By a process substantially similar to that of example 5, 2.9g of N-[3-(diethylamino)propyl]-4-(2-pyridinyl)-5-(3-pyridinyl)-1H-pyrazole-1-acetamide dihydrochloride was obtained from 2g (6.5 mmol) of ethyl 4-(2-pyridinyl)-5-(3-pyridinyl)-1H-pyrazole-1-acetate of example 3 and 3.1 mL (19.5 mmol) of 3-(diethylamino)propanamine. The free base was converted to the dihydrochloride by dissolving in ethanol, adding excess HCl in ether, and recrystallizing the resulting solid from ethanol-ether to yield 2.6g of product, mp 149-150° C.

Example 8

N-[3-(Diethylamino)propyl]-4,5-bis(2-pyridinyl)-1H-pyrazole-1-acetamide

By a process substantially similar to that of example 5 it is contemplated that N-[3-(diethylamino)propyl]-4,5-bis(2-pyridinyl)-1H-pyrazole-1-acetamide may be synthesized from ethyl bis(2-pyridinyl)-1H-pyrazole-1-acetate of example 4 and 3-(diethylamino)propanamine.

Example 9

N-[3-(Diethylamino)propyl-5-(3-methoxyphenyl)-N-methyl-4-(4-pyridinyl)-1-acetamide

By a process substantially similar to that of example 5, it is contemplated that N-[3-(diethylamino)-propyl]-5-(3-methoxyphenyl)-N-methyl-4-(4-pyridinyl)-1H-pyrazole-1-acetamide may be synthesized from ethyl 5-(3-methoxyphenyl)-4-(4-pyridinyl)-1H-pyrazole-1-acetate and N-methyl-N′,N′-diethyl-1,3-propanediamine. It is anticipated that the desired ester may be synthesized from 4-picoline and m-anisoyl chloride by the methods of procedures 1 and 2, followed by a process substantially similar to example 1.

Example 10

N-[3-Diethylamino)-2-hydroxypropyl]-4-(4-fluorophenyl)-5-(4-pyridinyl)1H-pyrazole-1-acetamide

By a process substantially similar to that of example 5, it is contemplated that N-[3-(diethylamino)-2-hydroxypropyl]-4-(4-fluorophenyl)5-(4-pyridinyl)-1H-pyrazole-1-acetamide may be snythesized from ethyl 4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazole-1-acetate and 1-amino-3-(diethylamino)-2-propanol. It is anticipated that the desired ester may be synthesized from 1-(4-pyridinyl)-2-(4-fluorophenyl)ethanone [Lantos et al. J. Org. Chem. 53,4223 - 4227(1988)]by a process substantially similar to that of example 1 or example 4.

Other embodiments of the invention may be synthesized from the appropriate 4,5-diaryl-1H-pyrazole-1-acetates. The starting materials for compounds of the invention having varying R^1, R^2 and R^3 are described in copending U.S. application DN 7398C of Denis Bailey, which is incorporated herein by reference.

The antiarrhythmic activity of compounds of the invention was demonstrated by the following procedure.

Duncan Hartley guinea pigs (600-900 grams) of either sex were anesthetized with urethane (1.4 g/kg, i.p.) and supplemented as needed. An intravenous route for drug administration was established using microbore tubing inserted into the jugular vein. The induction of arrhythmias by aconitine hydrochloride (34

g/kg) was evaluated in control guinea pigs given 1 cc saline as an intravenous bolus 10 minutes prior to aconitine challenge.

Compounds to be tested were administered intravenously 10 minutes prior to aconitine challenge at an initial dosage of 30 mg/kg. This dosage was reduced in subsequent animals if severe cardiac rhythm disturbances persisted beyond two minutes after injection in the first guinea pig tested. All drugs were tested at the maximally tolerated dose (identified by the lack of arrhythmias in the EKG prior to aconitine challenge). Compounds were administered in saline as 1 cc bolus injections (n=5-9).

Time intervals between aconitine injection and the appearance of arrhythmias were determined. Specifically noted was the time until the onset of (i) the first premature ventricular contraction (PVC); (ii) the first sustained run of ventricular tachycardia consisting of 10 or more ventricular beats (VTACH); and (iii) the time until the appearance of ventricular fibrillation lasting longer than 15 seconds (VFIB). The average time and standard error of the mean until the appearance of these arrhythmias were calculated for each treatment group and compared to concurrent controls using a one-way analysis of variance. Activity was defined as a statistically significant delay in the onset of PVC, VTACH and VFIB time course compared to control values.

The following table summarizes the results obtained from the testing of representative compounds of the invention.

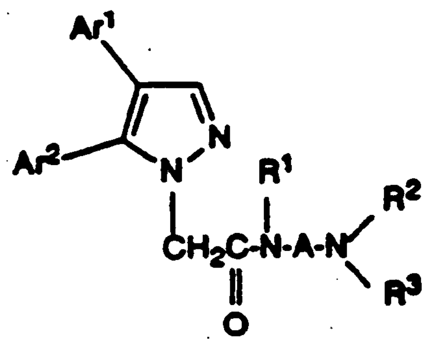
Example No.	Minutes to		
	PVC	VTACH	VFIB
Control	1.0-1.2	1.0-2.0	4.0-6.0
5	18.9	23.2	44.9
6	7.6	16.2	19.9
7	10.2	60.0	60.0

The compounds of the invention can be prepared for use by conventional pharmaceutical procedures: that is, by dissolving or suspending them or their pharmaceutically acceptable salts in a pharmaceutically acceptable vehicle, e.g., water, aqueous alcohol, glycol, oil solution or oil-water emulsion, for parenteral or oral administration;or by incorporating them in unit dosage form as capsules or tablets for oral administration either alone or in combination with conventional adjuvants or excipients, e.g., calcium carbonate, starch, lactose, talc, magnesium stearate, gum acacia, and the like.

The percentage of active component in the composition and method for treating or preventing arrhythmia can be varied so that a suitable dosage is obtained. The dosage administered to a particular patient is variable depending upon the clinician's judgement using as the criteria: the route of administration, the duration of treatment, the size and condition of the patient, the potency of the active component, and the patient's response thereto. An effective dosage amount of active component can thus be determined by the clinician considering all criteria and utilizing his best judgement on the patient's behalf.

Claims

1. A compound of formula



or acid-addition salt thereof wherein R^1 is hydrogen or lower-alkyl; R^2 and R^3 are independently hydrogen, lower-alkyl, or hydroxy lower-alkyl; or R^2 and R^3 together form a straight or branched alkylene chain of four to six carbons; A is $CH_2CH(OH)CH_2$ or $(CH_2)_n$ wherein n is an integer from two to eight; Ar^1 and Ar^2 are independently pyridinyl, phenyl, or phenyl substituted with methoxy, hydroxy or halogen; and at least one of Ar^1 and Ar^2 is pyridinyl.

2. A compound according to claim 1, wherein Ar^1 and Ar^2 are independently pyridinyl or phenyl.

3. A compound according to claim 2, wherein R^1 is hydrogen.

4. A compound according to claim 3, wherein A is $(CH_2)_3$.

5. N,N-[3-(Diethylamino)propyl]-5-phenyl-4-(2-pyridinyl)-1H-pyrazole-1-acetamide or an acid addition salt thereof according to claim 4.

6. N,N-[3-(Diethylamino)propyl]-4-phenyl-5(3-pyridinyl)-1H-pyrazole-1-acetamide or an acid addition salt thereof according to claim 4.

7. N-[3-(Diethylamino)propyl]-4-(2-pyridinyl)-5-(3-pyridinyl)-1H-pyrazole-1-acetamide according to claim 4.

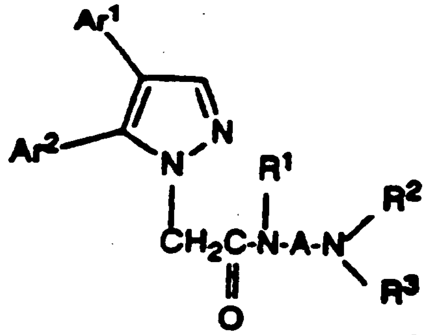
8. A process for preparing a compound according to claim 1, which comprises reacting a compound of the Formula IV (herein) where R^4 is lower-alkyl or hydrogen with:
a. a compound of the Formula V (herein) to prepare a corresponding compound of Formula I or
b. a compound of the Formula VI (herein) to prepare a corresponding compound of the Formula VII (herein), and reacting said latter compound obtained with an agent capable of converting the alcoholic function to a group suitable for nucleophilic attack to prepare a corresponding compound of Formula VIII (herein), and reacting the latter compound with a compound of Formula IX (herein) so as to obtain the corresponding compound of Formula I where A is $(CH_2)_n$, wherein X is a group subject to nucleophilic displacement,
and when R^4 is hydrogen, said free acid is activated prior to reacting with the compound of Formula V or VI,
and, if desired, converting a free base obtained into an acid-addition salt thereof.

9. A composition for treating cardiac arrhythmias comprising a compound according to any one of claims 1-7, in an amount effective to treat cardiac arrhythmias together with one or more pharmaceutically acceptable excipients or diluents.

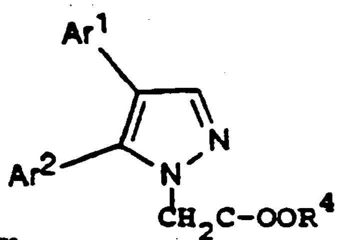
10. The use of a compound according to any one of claims 1-7, in preparing a medicament useful for treating cardiac arrhythmias in a susceptible subject.

Claims for the following Contracting States: ES, GR

1. A process for preparing a compound of formula



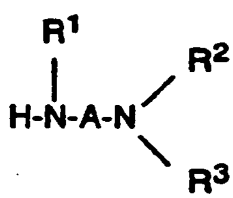
or acid-addition salt thereof wherein R^1 is hydrogen or lower-alkyl; R^2 and R^3 are independently hydrogen, lower-alkyl, or hydroxy lower-alkyl; or R^2 and R^3 together form a straight or branched alkylene chain of four to six carbons; A is $CH_2CH(OH)CH_2$ or $(CH_2)_n$ wherein n is an integer from two to eight; Ar^1 and Ar^2 are independently pyridinyl, phenyl, or phenyl substituted with methoxy, hydroxy or halogen; and at least one of Ar^1 and Ar^2 is pyridinyl, which comprises reacting a compound of the Formula IV



IV

where R^4 is lower-alkyl or hydrogen with:

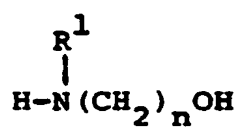
a. a compound of the Formula V



V

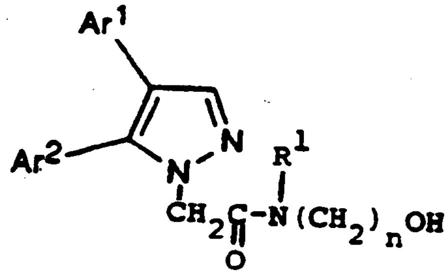
to prepare a corresponding compound of Formula I or

b. a compound of the Formula VI



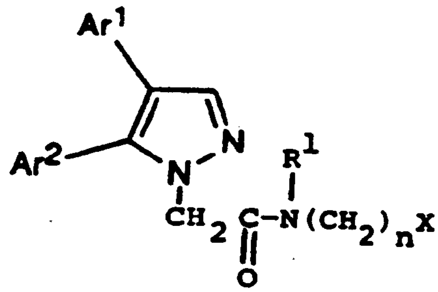
VI

to prepare a corresponding compound of the Formula VII



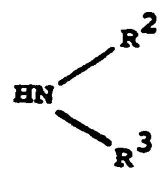
VII

and reacting said latter compound obtained with an agent capable of converting the alcoholic function to a group suitable for nucleophilic attack to prepare a corresponding compound of Formula VIII



VIII

and reacting the latter compound with a compound of Formula IX



IX

so as to obtain the corresponding compound of Formula I where A is $(CH_2)_n$, wherein X is a group subject to nucleophilic displacement,
and when R^4 is hydrogen, said free acid is activated prior to reacting with the compound of Formula V or VI,
and, if desired, converting a free base obtained into an acid-addition salt thereof.

2. A process according to claim 1, wherein Ar^1 and Ar^2 are independently pyridinyl or phenyl.

3. A process according to claim 2, wherein R^1 is hydrogen.

4. A process according to claim 3, wherein A is $(CH_2)_3$.

5. A process according to claim 4, for preparing N,N-[3-(diethylamino)propyl]-5-phenyl-4-(2-pyridinyl)-1H-pyrazole-1-acetamide or an acid addition salt thereof.

6. A process according to claim 4, for preparing N,N-[3-(diethylamino)propyl]-4-phenyl-5-(3-pyridinyl)-1H-pyrazole-1-acetamide or an acid addition salt thereof.

7. A process according to claim 4, for preparing N-[3-(diethylamino) propyl]-4-(2-pyridinyl)-5-(3-pyridinyl)-1H-pyrazole-1-acetamide.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 10 4125

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	EP-A-0 299 407 (STERLING DRUG INC.)		C 07 D 401/04 A 61 K 31/415 A 61 K 31/44
D,A	US-A-4 072 498 (M.W. MOON et al.)		
D,A	US-A-4 182 895 (D.M. BAILEY)		
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 D 231/00 A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	21-05-1990	DE BUYSER I.A.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document